Multiple Myeloma & Renal Disease

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Objectives

- Describe the patterns of renal involvement in multiple myeloma and their clinical and histological characteristics
- Relate the natural history of the various types of renal lesions in multiple myeloma
- Outline a diagnostic strategy for renal disease in multiple myeloma
- Describe current treatments for renal disease in multiple myeloma

Overview

1 Introduction
2 Patterns of renal disease
3 Usefulness of renal biopsy
4 Efficacy of plasmapheresis
5 Results of chronic dialytic support

Introduction

- renal failure predicts poor prognosis in patients with myeloma
  - historical 2mo survival
  - current $\leq$ 2yr survival (9-20mo)
- ~50% improve with chemo
- prognosis correlates with extent of tumor & response to chemotherapy

Myeloma and ARF
MacLennan, BMJ, ‘94

- Medical Research Council report on 998 consecutive patients with myeloma entered into trial btw.‘82-91:

  scr > 200umol/l - 18%

  scr > 130umol/l - 42%

  - most improve/return to normal in 3mo independent of LC excretion

Patterns of Renal Involvement

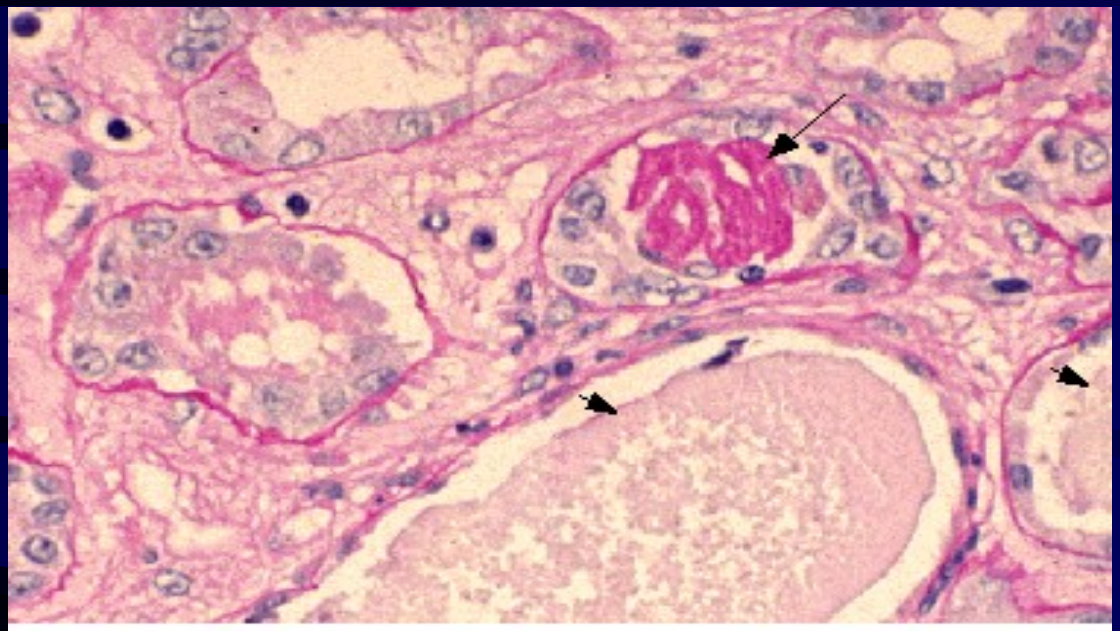
Brenner & Rector, The Kidney, ‘96

- myeloma kidney - 80%
- light chain deposition disease - 5-10%
- amyloid (AL) - 10%
- tubular lesion: hypercalcemia, volume depletion
- plasma cell infiltration
- cryoglobulinemia
- MGUS

Myeloma Kidney
A.K.A. Cast Nephropathy

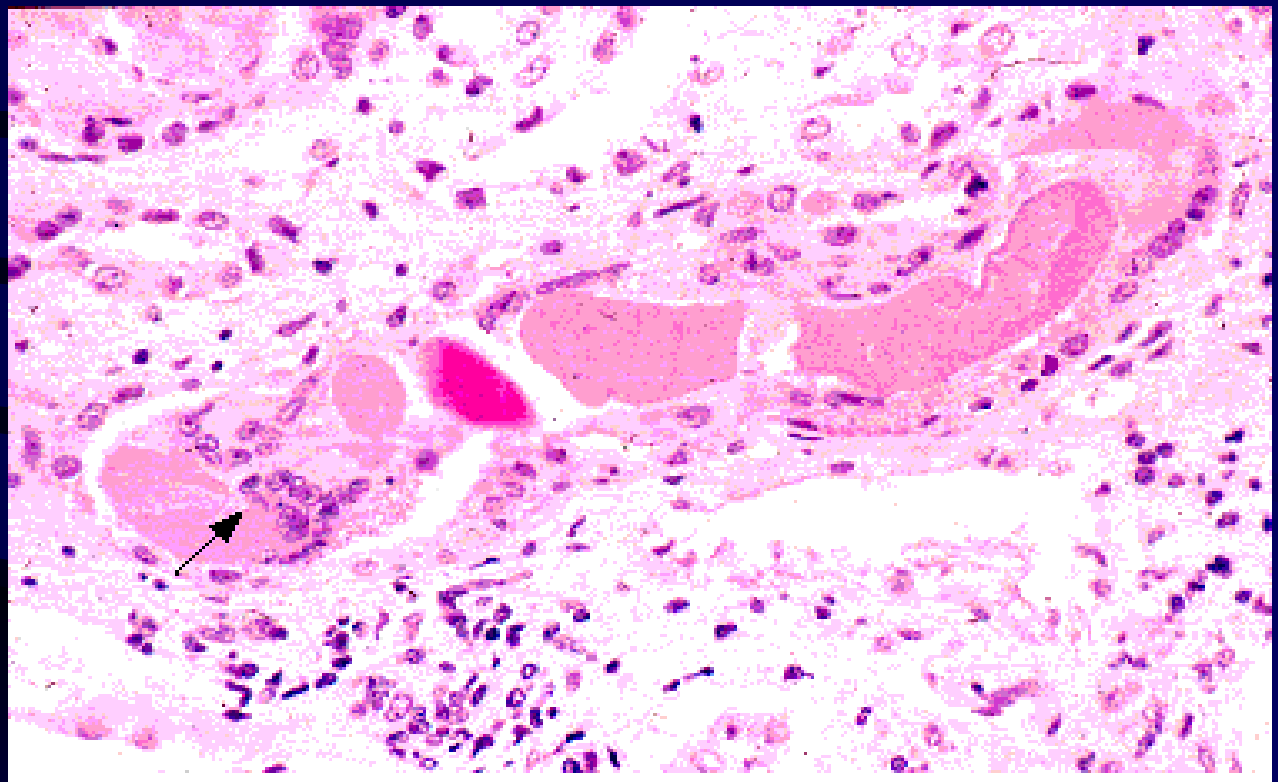
- fractured eosinophilic casts in the distal tubule
- giant cell reaction
- tubulointerstitial nephritis/fibrosis
- primary involvement is not glomerular:
  overflow proteinuria
  nephrotic syndrome is not present
- light chains almost always present

Cast Nephropathy



High power light micrograph showing PAS stain of tubular casts in myeloma kidney. The bottom two tubules contain casts composed of PAS-negative immunoglobulin light chains (small arrows). In comparison, the cast in the middle tubule (probably hyaline) is primarily composed of PAS-positive Tamm-Horsfall mucoprotein, the matrix of all casts (large arrow). Myeloma proteins are PAS-negative because they contain few of the neutral sugars that are detected by this stain. Courtesy of Helmut Rennke, MD.

Cast Nephropathy



Light micrograph showing obstructed tubule with a fractured dense cast in myeloma kidney. There is a giant cell reaction in the lower left part of the tubule induced by migration of interstitial macrophages into the tubule (arrow). Courtesy of Helmut Rennke, MD.

Cast Nephropathy
Etiology

- light chains (22kD) freely filtered
- receptor-mediated endocytosis in PT
- PT epithelial damage due to collection in endolysosomal system
- cast precipitation in DT & CT with obstruction & inflamation
- toxicity related to light chains (Bence Jones)

Light Chain Toxicity
Sanders, The Kidney 1993

- net isoelectric point (pI)
  pI < 5.1 do not self-aggregate, yet…
  not all cationic BJP's are toxic
- concentration of BJP in DT
- carbohydrate content of Tamm-Horsfall protein
- intraluminal Ca++ & pH
- tubular flow rate & NaCl content (diuretics)

Sanders, The Kidney, ‘93, cont’d

- self-aggregation of THP promoted by [NaCl] > 60-80mM, increasing [Ca+2] or [H+]
- THP serves as the nidus for BJP cast formation

Pathobiology of Cast Nephropathy

Sanders, JCI, '92

- utilized *in vivo* nephron perfusion in rats
- infused several isolated human BJP's from patients with cast nephropathy
- evaluated effects of BJP concentration, mild volume depletion, addition of furosemide, and addition of/pretreatment with colchicine

Sanders, JCI, ‘92, cont’d

results:

1. distal nephron obstruction was BJP concentration-dependent, assessed by perfusion pressure & confirmed by nephron dissection
2. casts seen in TALH or MCT, never proximal
3. limited hydration resulted in cast formation even with “non-toxic” BJP’s, earlier with toxic BJP’s

Sanders, JCI, ‘92, cont’d

4. furosemide caused concentration-dependent THP self-aggregation as assessed by turbidity studies
5. furosemide accelerated rate of obstruction of artificially perfused nephrons in concentration-dependent fashion
6. colchicine limited the THP self-aggregation

Sanders, JCI, ‘92, cont’d

7. colchicine decreased urinary THP excretion, and decreased the amount of carbohydrate in THP
8. THP isolated from rats pretreated with colchicine did not aggregate with BJP
9. systemic treatment with colchicine prevented LC cast formation in perfused nephrons of rats
10. *b*-lumicolchicine had limited effects

Bence Jones Protein Binding
Huang, JCI, '93

- goal: examine binding of BJP to THP
- method:

  isolated BJP's from 5 pts with MM & ARF

  ELISA & binding curves of various BJP's

  competitive inhibition of THP binding

  reducing agents & deglycosylation used to alter THP conformation & binding

Huang, JCI, ‘93, cont’d

- results:
  BJP’s bind with varying affinities & rates
  binding affinity is not related to pI of BJP
  THP peptide region is common binding site
  THP binding correlated with BJP aggregation
  reducing agents partially blocked binding
  deglycosylation of THP blocked aggregation

Huang, JCI, ‘93, cont’d

- conclusions:

  carbohydrate moiety of THP (sialic acid) is essential in heterotypic aggregation of THP & BJP

  THP-BJP coaggregation can be altered

  pI may be important in coaggregation of THP with BJP

Therapy to Prevent Cast Formation

- chemotherapy to decrease BJP production
- 2-3 l/d free water intake
- avoidance of diuretics, radiocontrast, toxins
- correction of hypercalcemia
- urinary alkalinization
- ? plasmapheresis
- ? colchicine or reducing agents

Renal Failure in Myeloma
Alexanian, Arch Int Med, '90

- analysis of 494 patients with newly diagnosed MM btw. 1974-89 at MD Anderson
- all rec'ed similar doxorubicin-based chemo.
- variables: tumor load

  response (75% fall in PC mass, no BJP)

  ARF (scr > 180umol/l at dx)

  renal improvement (scr ≤ 120umol/l)

Alexanian, Archives, ‘90, cont’d

- ARF present in 89/494 (18%) overall (no biopsies), only 3% had low tumor burden
- Ca & BJP were independent risk factors - 97%
- no difference in *k* versus *l* LC
- 51% of ARF reversible over 1-4mo
- only high tumor mass had poor survival effect
- ARF correlated with extent of MM

Myeloma with Renal Involvement

Ganeval, Nephrology, ‘92

- retrospective review btw. ‘65-90
- 80 patients with myeloma & severe ARF:
  95% had Bence Jones proteinuria & 50% only BJP
- nearly 50% had precipitating factor in ARF
- 19/30 biopsied had cast nephropathy, 8 had amyloid, 8 had LCDD (some overlap)

Ganeval, Nephrology, ‘92, cont’d

- outcome:

  50% had improvement in renal function

  good correlation btw renal function @ 1mo & long-term prognosis

  most patients with precipitating event improved

  response to chemo, renal function @ 1mo & clinical stage were predictive of survival

Precipitants of Renal Failure

- 50-97% of those with ARF had precipitating factors:
  hypercalcemia
  volume depletion
  radiocontrast
  NSAID’s
  Ganeval ‘92, Bernstein ‘82, Alexanian ‘90

Treatment Options

- traditional-

  melphalan & prednisone, 40% response rate
- alternative-

  VAD - faster remission, 15% response, hepatic metabolism

  CTX & prednisone
- +/- plasmapheresis

Theoretical Benefits of Plasmapheresis

- rapid removal of LC, although LC distribute thruout extracellular volume so small net effect
- reduction of plasma hyperviscosity
- exchange of normal for abnl immunoglobulins
- removal of “factors” which inhibit neutrophils
- removal of “factors” which promote myeloma proliferation

Plasmapheresis in Myeloma
Zuchelli, KI, '88

- prospective study of 29 pts with ARF (scr $\geq$ 5mg/dl) & MM btw. 1980-86
- 17/29 renal biopsy with 16/17 cast nephropathy
- 20/29 with LC myeloma
- randomized to steroids/CTX $\pm$ TPE (5x1PV)
- Grp 1 - TPE & hemodialysis (n=15)

  Grp 2 - no TPE & peritoneal dialysis (n=14)

Zuchelli, KI, ‘88, cont’d

- response = fall in scr ≥ 25% & dialysis d/c’ed
- baseline scr 9-11mg/dl, 55% oliguric, stage III
- results:

  Grp 1 - 11/13 off dialysis, mean scr 2.6mg/dl at 2mo, 9/15 with 12mo survival

  Grp 2 - 2/11 off PD, scr 7.7mg/dl, 3/14 survival at 12mo

Zuchelli, KI, ‘88, cont’d

- no deaths from uremia - majority due to cancer or infection
- conclusion:

  plasmapheresis is effective in ARF & MM in improving renal function & survival
- problems include different modes of dialysis, very high death rate in Grp 2, poor survival

Plasmapheresis in ARF & Myeloma
Johnson, Arch Int Med, '90

- prospective study of 21 pts. with ARF & MM
- ARF = oliguria & rising scr or scr > 270umol/l
- renal bx 16/21 - 50% severe myeloma kidney
- Grp 1 - M/P

  Grp 2 - M/P + TPE (1PV tiw x 1-4wks, 5% alb)
- hemodialysis at presentation in 5/10 vs. 7/11

Johnson, Archives, ‘90, cont’d

- results:

  renal recovery in 5/10 *v* 7/11 (NS)

  5/5 *v* 4/7 on HD at entry reached ESRD

  TPE offered no survival benefit

  20% 2-year survival

  2/7 with severe myeloma kidney recovered renal function *v* 7/9 with primarily TIN

Johnson, Archives, ‘90, cont’d

- conclusions:

  chemotherapy & supportive therapy should be initiated

  renal biopsy should be performed in those with progressive deterioration

  TPE should be offered to those without severe cast formation or chronicity

Plasmapheresis in myeloma

Zucchelli, et al	Controls (N=14)a	Plasma Exchange (N=15)b
Dialysis Dependent, recovered	11(2)	13(11)
Oliguric	8	8
Improved or stable	5	13
Death <2 months	5	1

Johnson et al	N=10	N=11
Initial Creatinine (μmol/L) (SD)	130±300	880±540
Dialysis-dependent, recovered	5(0)	7 (3)
Oliguric, recovered	1(0)	4(3)
Long-term dialysis	5	4

A=Peritoneal dialysis alone b=Hemodialysis and Plasma Ecchange

Long-term Survival
Pasquali, Clin Neph ‘90

- retrospective review of 37 pts followed prospectively for 36mo or until death:

  Grp 1 - 27 died < 1 yr

  Grp 2 - 10 survived > 36 mo

  (24 patients from prospective TPE trial included)
- 30/37 renal biopsy with 25/30 myeloma kidney
- variables - LC, b2m, Ca, pI, biopsy, tumor mass

Pasquali, Clin Neph, ‘90, cont’d

- Grp 1 - hypercalcemia, infection < 2mo, biopsy-proven chronicity & severe cast formation were poor prognostic indicators
- renal recovery - 30% in Grp 1 *vs* 80% in Grp 2
- high early death rate in Grp 1 (12/27 in 2mo)
- TPE patients were equally divided btw groups
- most deaths due to infection & cancer cachexia

End Stage Renal Disease in Myeloma

- 1996 USRDS reported 255,000 new cases of ESRD for ‘91-93:

  myeloma accounted for 2095 (0.9%)

  1yr mortality overall 22.2%

  myeloma & ESRD had 1yr mortality ~ 50%
- however, overall survival reflects survival due to myeloma & is little altered by renal failure

Outcome of ESRD in Myeloma
Port, QJM, ‘89

- reviewed HCFA data from ESRD Networks, accounting for ~ 80% of dialysis population
- 731patients (1.14%) initiated btw 1/83 - 12/85
- primary mode of RRT was in-center HD
- 1yr survival of 54%; 30mo survival of 25%
- 5.1% late renal recovery
- MM is the 1st neoplasm for which RRT is rec’d

Forms of Renal Replacement Therapy

- dialysis - both hemodialysis and peritoneal dialysis (IPD, CAPD) have been used
- complications are primarily infectious with high incidence of catheter/line infection
- renal transplant reported in 9 patients

Hemodialysis vs. Peritoneal Dialysis

considerations:

- increased bleeding risk
- high number of infectious complications
- PD removes larger amount of Ig & free LC

Peritoneal Dialysis in Myeloma

Korzets, AJKD, '90

- review of 10 patients with MM & renal failure who remained dialysis-dependent > 2mo
- CAPD used as initial therapy:

  6 required dialysis at presentation

  4 began on dialysis 7-48mo after diagnosis
- results:

  CAPD duration of 1-66mo (mean 20)

Korzets, AJKD, ‘90, cont’d

3 pts transfered to hemodialysis
peritonitis 1 episode per 5.6 patient-months
mean survival after diagnosis in 5 responders
47mo *vs* 17mo in non-responders
mean survival after dialysis initiated 25mo
death - MM, infection, withdrawal of care
hospitalization 75 days/year/patient

Renal Transplant in Myeloma

Sammett et al, Transplantation, ‘96

- 9 patients with low-grade, successfully treated, or previously undiagnosed MM underwent CRT
- avg. survival of 35mo (range 14-96mo) s/p CRT
- all patients had good renal function at time of death
- conc: MM was not an absolute contraindication to CRT if low-grade or stable disease is present

Conclusions

1. Myeloma is not an uncommon cause of ARF, CRF, and ESRD.
2. Patients may present to the nephrologist with severe degrees of azotemia.
3. ~ 50% of ARF in setting of myeloma is reversible, although prolonged dialysis may be necessary.

4. Degree of renal dysfunction may correlate with prognosis as a measure of myeloma severity.
5. There is a suggestion that plasmapheresis may be effective in certain patients (little chronicity, high LC, rising scr).
6. No data exists to suggest that PD or HD is more efficacious.

7. Renal biopsy should be performed prior to TPE.
8. Given a reasonable 1-2yr survival, dialysis should be offered if effective chemotherapy is available.
9. Renal transplant should be considered very rarely, if at all, in myeloma & ESRD.